Complete Summary

GUIDELINE TITLE

Genetic counseling for fragile X syndrome: recommendations of the National Society of Genetic Counselors.

BIBLIOGRAPHIC SOURCE(S)

McIntosh N, Gane LW, McConkie-Rosell A, Bennett RL. Genetic counseling for fragile X syndrome: recommendations of the National Society of Genetic Counselors. J Genet Counsel 2000;9(4):303-25.

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

Fragile X syndrome (also known as Martin-Bell syndrome, marker X syndrome, and FRAXA syndrome)

GUIDELINE CATEGORY

Counseling
Risk Assessment

CLINICAL SPECIALTY

Medical Genetics

INTENDED USERS

Advanced Practice Nurses
Health Care Providers
Nurses

Physician Assistants
Physicians

GUIDELINE OBJECTIVE(S)

To assist health care professionals who provide genetic counseling for individuals and families in whom the diagnosis of fragile X syndrome is strongly suspected or has been made.

TARGET POPULATION

Patients in whom the diagnosis of fragile X syndrome is strongly suspected or has been made.

INTERVENTIONS AND PRACTICES CONSIDERED

1. Assessment, including family history, medical history of proband, pregnancy history of at-risk carriers, and psychosocial history of the consultand.
2. Education/health promotion.
3. FMR1 gene testing.
4. Risk assessment by analysis of the pedigree and FMR1 DNA test results.
5. Genetics management, including FMR1 testing of additional relatives.
6. Psychological support and referral.
7. Address ethical issues including testing on health unaffected minors and family members.
8. Follow-up with genetic test results, other support resources, referrals.

MAJOR OUTCOMES CONSIDERED

Not stated

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Secondary Sources)
Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

The guideline developers searched the National Library of Medicine's MEDLINE database to locate relevant English language medical articles published between 1990 and 1999. The authoring subcommittee reviewed these articles with attention to genetic counseling issues. The literature is based on clinical experience, descriptive studies, and/or reports of expert committees. The authoring subcommittee also reviewed policy statements published by the American College of Medical Genetics and guidelines drafted by genetic providers in Washington State.

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

The literature was reviewed and evaluated for quality according to the categories outlined by the U.S. Preventative Services Task Force (1995):

I. Evidence obtained from at least one properly designed randomized controlled trial.

II-1. Evidence obtained from well-designed controlled trials without randomization.

II-2. Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one center or research group.

II-3. Evidence obtained from multiple time series with or without the intervention.

III. Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.

METHODS USED TO ANALYZE THE EVIDENCE

Systematic Review

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Not applicable

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

The recommendations are the opinions of genetic counselors with expertise in Fragile X Syndrome counseling and are based on clinical experience, a review of pertinent English language medical articles, and reports of expert committees.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

External Peer Review
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

A draft document was mailed to the 1,613 members of the National Society of Genetic Counselors (NSGC) for comment. The NSGC membership includes genetic counselors, physicians, nurses, attorneys, doctors of philosophy, and students. The revised document was reviewed by the NSGC attorney and the NSGC Ethics Subcommittee (comprising eight genetic counselors), and no conflicts with the NSGC Code of Ethics or issues regarding legal liability were identified in the final document. All 21 members of the NSGC Board of Directors reviewed and unanimously approved the final document in October, 1999.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Primary Counseling Considerations: Fragile X Syndrome (FXS)

Comprehensive FXS genetic counseling for individuals and families in whom the diagnosis of FXS is strongly suspected or has been made may require several sessions (especially when counseling learning-disabled individuals) and may involve a long-term commitment on the part of the genetic counselor to follow families. If this commitment cannot be made, referring the family to an experienced FXS genetic counselor or program should be considered.

I. Assessment

Ascertain the client's primary questions and concerns.
Mutually develop a plan to address concerns.

A. Family History
   1. Using standardized pedigree symbols, obtain a comprehensive three- or more generation pedigree from the proband/consultand (e.g., offspring, siblings' offspring, parents, grandparents, aunts, uncles, nieces, nephews, and first cousins), if possible.
      a. If information is known about maternal and paternal grandparents' relatives, this information should be recorded. Those relatives are at risk of being carriers/affected with FXS.
      b. Note ethnic background, consanguinity, and ongoing pregnancies.

2. Determine which family members are known to be or are suspected of being affected with FXS or of being carriers of an FMR1 gene mutation.
    a. Verify with medical records, if possible. Clarify and record whether or not the individual(s) has/have had cytogenetic testing, or FMR1 gene analysis by polymerase chain reaction (PCR)/Southern Blot. If the diagnosis was made by cytogenetic testing, FMR1 gene analysis is recommended to confirm the diagnosis and to rule out FRAXE and FRAXF.
3. Note if family members have mental retardation, learning disabilities, autism, developmental delay, attention deficit disorder (ADD), attention deficit hyperactive disorder (ADHD), dysmorphic features, mitral valve prolapse, seizures, sudden infant death syndrome (SIDS).
    a. Verify with medical records, if possible.
4. Note if female relatives have a history of symptoms that may be related to an FMR1 gene mutation (e.g., premature menopause, ovarian cysts, irregular periods, shyness, gaze avoidance, problems with math, excessive worrying, sleep disturbances, mood swings, obsessive-compulsive behavior, social anxiety, impulsivity, depression, counseling or medication for emotional or behavioral difficulties).
5. Note if male relatives have a history of symptoms that may be related to an FMR1 gene mutation (e.g., anger outbursts, solitary behavior, hyperactivity, hand flapping, gaze avoidance, large testicles).
6. Maintain family history with respect to confidentiality of consultand, proband, and extended family members.

B. Medical History of Proband

Inquire about:

1. Medical conditions (e.g., ADHD, ear infections and patulous eustachian (PE) tubes, reflux, hypotonia, hyperactive gag reflex, kidney and/or ureter problems, strabismus, cardiac murmur, FTT, seizures, sleep apnea, hernias).
2. Medication history.
3. Hospitalizations, birth defects, developmental history (delayed fine and gross motor skills, delayed speech and language development).
4. Tactile defensiveness, hand flapping, gaze avoidance, feeding problems, behavioral outbursts, aggressive behavior, any autistic features, and/or echolalia.
5. Findings from the clinical examination of the patient (large testicles, large or prominent ears, long face, scoliosis, evaluation of joint mobility, eye problems, informal assessment of social skills).
6. Findings of developmental testing/psychometric and school evaluations.
7. History of neglect or abuse.
8. Verify above information with medical records, if possible.

9. Maintain medical record in a confidential manner according to employing institution´s policy

C. Pregnancy History of At-Risk Carriers

Record:

1. Gravidity, parity, termination of pregnancy (TOP), spontaneous abortion (SAB).
2. Menstrual history/premature ovarian failure (POF).
3. Difficulty in conceiving and use of reproductive intervention.
4. Unusual environmental exposures or complications during pregnancy.
5. Prenatal testing and results.

D. Psychosocial History of the Consultand

Assess, record and address:

1. Emotional and behavioral features that may be related to an FMR1 gene mutation.
2. Level of comprehension and communication.
3. Level of education, employment, and social functioning, if appropriate.
4. Perceived burden of disease and risk perception.
5. Coping skills.
6. Family/community support structure.
7. Attempt to build a relationship with the consultand by validating, empathizing, and listening.

II. Education/Health Promotion

A. Discuss the clinical presentation of FXS in males and females.

B. Discuss follow-up recommendations (e.g., identification and testing of at-risk family members, scheduling for follow-up visits).

C. Discuss the genetics of FXS and approach to testing (including risks for expansion or reversion, and anticipation, if appropriate).
1. FMR1 testing, which should include a discussion of the CGG repeat, methylation, sensitivity, and specificity.
2. Inheritance pattern, including examples of females and males with the premutation and full mutation, and the risk of expansion/reversion in such cases.
3. Reproductive options and testing (e.g., adoption, donor egg or sperm, prenatal diagnosis); include ethical concerns raised by such options, if appropriate.
4. Cost of testing and test limitations.
5. Routine cytogenetic testing, if indicated.

D. Be able to answer general questions relating to suggested treatment, therapy, and the function of the FMR1 protein, and be prepared to make appropriate referrals regarding topics which do not fall within the scope of genetic counseling practice.

III. Risk Assessment

A. Analyze the pedigree and FMR1 DNA results to assess and address:
1. The consultand´s FMR1 gene status.

2. The FMR1 gene status or risk to have inherited an FMR1 gene mutation for the consultand´s first-degree relatives, if appropriate.

B. Discuss possible genetic counseling referrals for other family members for FXS risk assessment, if appropriate.

IV. Genetics Management

A. Facilitate confirmation of the diagnosis in suspected/affected family members and/or suspected/obligate female carriers via FMR1 gene analysis, if indicated and testing is accepted. This process should be tailored to meet the needs of each consultand. In general however, offering FMR1 gene analysis proceeds in a sequence to contain costs. (See Figure 1 in the guideline document.)

B. If the FMR1 gene test is positive (+) in a relative, testing should be considered in additional relatives of this individual. If the gene test is negative (-), no further FMR1 gene testing is suggested for that branch of the family.

C. When offering testing to other family members, it may be necessary to refer relatives to other genetic counselors due to geographical and other constraints.

D. The test results for daughters of a known transmitting male should not be inferred from their father´s results. There is a possibility of misattributed paternity or of gene reversion. Testing obligate carriers may help them to better understand their gene status, although some carriers may prefer not to have this information.

E. Facilitate prenatal diagnosis, if indicated (refer to "Clinical Management").

1. Use a laboratory that is CLIA certified and has prior experience with the interpretation of the FMR1 molecular patterns in prenatal specimens.

V. Psychological Issues

A. Assess/identify community resources for appropriate services and/or support.

B. Address psychological issues (e.g., denial, anxiety, obsessive-compulsive behaviors, anger, grief, guilt, blame, depression, isolation, inability to cope, hopelessness), when indicated.

C. Make referrals for more in-depth counseling, when necessary.

VI. Ethical Issues

A. Testing healthy unaffected minors (refer to "Age That Carrier Testing Should Be Done").

B. Misattributed parentage in initial assessment of risk, and FMR1 gene testing.

C. The implications and ramifications of testing or not testing family members who may prefer not to know their FMR1 gene status or do not wish their children to be aware of their risk.

D. How to inform other family members of their risk while respecting individual privacy.

E. Health and life insurance dilemmas relating to testing and the diagnosis, ideally before initiating testing, particularly in healthy individuals.

VII. Follow-Up

A. Arrange/facilitate additional appointments to complete the family history, risk assessment, testing considerations, and/or follow the medical progress of the patient, as indicated.

B. Devise a plan for reporting test results.
C. Provide genetic testing results.
D. Offer posttesting support counseling (by office visit or telephone).
E. Facilitate referrals to appropriate professionals (e.g., neurologist, psychologist, ophthalmologist, cardiologist, speech/language/occupational therapists who are experienced with sensory integration techniques), if indicated.
F. Obtain outcome information on pregnancies that occur in the family, if possible.
G. Consider making available to the family a letter that will facilitate their informing family members of their risks (see the following section).
H. Offer genetic counseling of referrals to other genetic counselors, for family members.
I. Provide the family with names of support groups/resources (refer to Table III in the guideline document).

VIII. Patient Letters

It is suggested that the consultand be offered a letter following the conclusion of the genetic counseling session(s) and testing. Letters should be tailored to each family and should include a summary of major topics discussed in the genetic counseling session(s). A letter serves the purpose of providing a permanent, easily understood record of the relevant information discussed, as well as relaying information that may have become available since the family´s last visit. The consultand may also choose to share the letter with other family members.

Special Cases/Exceptions to Practice Recommendations

I. Pregnant Consultand

When counseling a pregnant consultand with limited time to adequately address the full array of counseling considerations, the primary focus of discussion should be the clinical spectrum of FXS, prenatal testing options, ramifications of testing the pregnancy, and views regarding management of pregnancy. If possible, the pregnant consultand´s FMR1 status should be clarified and confirmation of an FMR1 mutation in an affected relative should be made before any invasive prenatal procedure is done. Furthermore, it is strongly suggested that only laboratories that are experienced with diagnosing FMR1 gene mutations prenatally be used for prenatal diagnosis of an FMR1 gene mutation (refer to "Genetics Management").

II. Counseling of an Affected Female

Considerations when counseling individuals with mental retardation are addressed in Finucaane citations provided in the guideline document.

III. Informing Minors of Their FMR1 Mutation Status

Refer to "Age That Carrier Testing Should Be Done". The mutation status of the daughters of transmitting males should not be assumed.

CLINICAL ALGORITHM(S)

A suggested FMR1 gene-testing flowchart is provided in the guideline document.

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The rating of supporting literature for this guideline is III [opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees]. See "Methods Used to Assess the Quality and Strength of Evidence" field.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Appropriate genetic counseling for fragile X syndrome.

Subgroups Most Likely to Benefit:

Pregnant females

POTENTIAL HARMS

None anticipated

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

1. The genetic counseling recommendations of the National Society of Genetic Counselors (NSGC) are developed by members of the NSGC to assist practitioners and patients in making decisions about appropriate management of genetic concerns. Each practice recommendation focuses on a clinical or practice issue and is based on a review and analysis of the professional literature. The information and recommendations reflect scientific and clinical knowledge current as of the publication date and are subject to change as advances in diagnostics techniques, treatments, and psychosocial understanding emerge. In addition, variations in practice, taking into account the needs of the individual patient and the resources and limitations unique to the institution or type of practice, may warrant approaches, treatments, or procedures alternative to the recommendations outlined in this document. Therefore, these recommendations should not be construed as dictating an exclusive course of management, nor does use of such recommendations guarantee a particular outcome. Genetic counseling recommendations are never intended to displace a health care provider´s best medical judgement based on the clinical circumstances of a particular patient.

2. The age at which it is appropriate to test or inform of the genetic risk in seemingly healthy individuals is a controversial topic and no consensus has been reached.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Living with Illness
Staying Healthy

IOM DOMAIN

Effectiveness
Patient-centeredness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

McIntosh N, Gane LW, McConkie-Rosell A, Bennett RL. Genetic counseling for fragile X syndrome: recommendations of the National Society of Genetic Counselors. J Genet Counsel 2000;9(4):303-25.

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2000

GUIDELINE DEVELOPER(S)

National Society of Genetic Counselors

SOURCE(S) OF FUNDING

National Society of Genetic Counselors

GUIDELINE COMMITTEE

Genetic Services Committee

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

Authors: Nathalie McIntosh, MSc (Children's Hospital, Boston, MA); Louise W. Gane, MS (Fragile X Treatment and Research Center); Allyn McConkie-Rosell, PhD (Duke University Medical Center); Robin L. Bennett, MS (Medical Genetics, University of Washington Medical Center).

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Not stated

GUIDELINE STATUS

The guideline developer states that an update is in progress at this time.

GUIDELINE AVAILABILITY

Electronic copies: Not available at this time.

Print copies: Available from the National Society of Genetic Counselors, 233 Canterbury Drive, Wallingford, PA 19086-7608; Web site: www.nsgc.org.

AVAILABILITY OF COMPANION DOCUMENTS

The following is available:

- Bennett RL, Steinhaus KA, Uhrich SB, et al. Recommendations for standardized human pedigree nomenclature. Am J Hum Genet 1995;56:745-52 and J Genet Couns 1995;4:267-79.

Electronic copies: Not available at this time.

Reprints available from Robin L. Bennett, Medical Genetics, Box 357720, University of Washington Medical Center, Seattle, WA 98195-7720.

PATIENT RESOURCES

The following is available:

National Society of Genetic Counselors. Genetic counseling: Valuable information for you and your family. Wallingford (PA): National Society of Genetic Counselors, 1995.

Print copies: Available from the National Society of Genetic Counselors, 233 Canterbury Drive, Wallingford, PA 19086-7608; Web site: www.nsgc.org.

particular patients. Rather we urge patients and their representatives to review this material and then to consult with a licensed health professional for evaluation of treatment options suitable for them as well as for diagnosis and answers to their personal medical questions. This patient information has been derived and prepared from a guideline for health care professionals included on NGC by the authors or publishers of that original guideline. The patient information is not reviewed by NGC to establish whether or not it accurately reflects the original guideline's content.

NGC STATUS

This summary was completed by ECRI on September 29, 2000. The information was verified by the guideline developer on October 27, 2000.

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